UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,345	06/19/2003	Andreas Gerardus Uitterlinden	ERUR121089	5017

26389 7590 03/14/2006

CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,345	UITTERLINDEN ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,29 and 30* is/are rejected.

7)☒ Claim(s) *5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 1-26, 29, and 30 filed 2/06/2006 is acknowledged.

2. The requirement for restriction is deemed proper and is therefore made FINAL.

3. Claims 27-28 are withdrawn from consideration.

4. Claims 1-26, 29, and 30 are currently under examination.

Claim Objections

5. Claim 5 objected to because of the following informalities: the preamble states a method of "determining bone fracture" whereas the last sentence is drawn to an "increased susceptibility to bone fracture". It appears "susceptibility" is missing from the claim preamble because all the other method steps are drawn to determining susceptibility to bone fracture. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-15 lack a positive process step relating back to the preamble. The preamble states a method of treating a mammalian subject. The last step is

determining the presence of a haplotype which is indicative of an increased susceptibility to bone fracture. It is unclear if this is a method of treatment or a method of determining susceptibility to bone fracture.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 1-26 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention</u>

Claims 1 and 2 are drawn to a method of determining susceptibility to a bone fracture in a mammalian subject comprising determining the presences of the px haplotype in the estrogen receptor alpha gene. Claim 3 is drawn to a method of determining susceptibility to bone fracture further comprising determining whether an allele of a vitamin D receptor gene is present. Claim 4 is drawn to a method of determining susceptibility to bone fracture further comprising analyzing the mammalian subject for at least one of the b, a, and T alleles in the vitamin D receptor gene. Claim 5 is drawn to a method of determining bone fracture wherein the presence of baT is indicative to an increased susceptibility to bone fracture. Claim 6 is drawn to a method of determining susceptibility to bone fracture compromising determining the copy number of the p, P, X, and x alleles of estrogen receptor alpha gene and the B, b, A, a, T, and t alleles of the vitamin D receptor gene. Claim 7 is drawn to comparing the estrogen receptor alpha gene alleles or vitamin D receptor gene alleles present in the mammalian subject with genotypes of the estrogen receptor alpha or vitamin D receptor genes having known degrees of risk of bone fracture. Claims 8-9 are drawn to a method performed in vitro and on a blood or tissue sample. Claim 10 is drawn to a mammalian subject suffering from low bone mineral density Claim 11 is drawn to a mammalian subject, which has a normal level of bone mineral density. Claims 12-13 are drawn to a method to prevent or reduce the risk of bone fracture, wherein the presence of the px haplotype is indicative of an increase susceptibility to bone fracture. Claim 14 is drawn to a method of treating a mammalian subject comprising determining which alleles are present in the vitamin D receptor gene and wherein the presence of a

haplotype comprising at least one of the b, a, and T alleles is indicative of an increased susceptibility to bone fracture. Claim 15 is drawn to a method of treating a subject comprising determining whether the baT haplotype of the vitamin D receptor gene is present. Claim 16 s drawn to a method of treating compromising determining the copy number of the p, P, X, and x alleles of estrogen receptor alpha gene and the B, b, A, a, T, and t alleles of the vitamin D receptor gene. Claim 17 is drawn to a method of treating comprising comparing the estrogen receptor alpha gene alleles or vitamin D receptor gene alleles present in the mammalian subject with genotypes of the estrogen receptor alpha or vitamin D receptor genes having known degrees of risk of bone fracture. Claim 18 is drawn to a method of treatment comprising at least one modification to lifestyle and administration of a pharmaceutical preparation effective to prevent or reduce the risk of bone fracture. Claim 19 and 20 are drawn to a human subject and a female subject. Claim 21 is drawn to a method of formulating a treatment regimen to decrease the risk of bone fracture in a mammalian subject comprising determining if the px haplotype is present. Claim 22 is drawn to a method of formulating a treatment regimen further comprising determining whether a baT haplotype is present. Claim 23 is drawn to a method of formulating a treatment regimen comprising comparing the estrogen receptor alpha gene alleles or vitamin D receptor gene alleles present with genotypes of the estrogen receptor alpha or vitamin D receptor genes having known degrees of risk of bone fracture. Claim 24 is drawn to administering a treatment effective to decrease the risk of bone fracture. Claim 25 is drawn to a method of determining susceptibility to bone fracture comprising using a kit to determine if the px haplotype is present. Claim

26 is drawn to a method of determining susceptibility to bone fracture comprising using a kit to determine if the px and baT haplotype is present. Claims 29 and 30 are drawn to a method to determine susceptibility of a bone fracture wherein the presences of the haplotype is determined by amplification of a portion of the first intron of the estrogen receptor alpha gene and amplification of the portion of the vitamin D receptor gene between exon 7 and 3' untranslated region.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts unexpected associations between specific Estrogen Receptor alpha gene (ERα) and vitamin D receptor (VDR) genotypes and the vertebral fracture (p. 3 lines 9-11). The specification asserts the term "bone damage" does not include low bone mineral density (BMD) (p. 9 lines 20-21). The specification does not teach how to differentiate fractures associated with BMD and fractures not associated with BMD.

The specification asserts that risk of susceptibility to bone damage is independent of bone mineral density (p. 9 lines 28-30). The specification asserts that there is a correlation between individuals with the p and x alleles and susceptibility to bone fractures (p. 11 lines 8-11). The specification asserts that the p and x alleles are specific polymorphisms in the ERα known as C397T and G351A (p. 11 lines 5-8). The

specification asserts a subject having the px haplotype in ERα and a haplotype of BAt or baT for the VDR polymorphisms is susceptible to bone fractures (p. 11 lines 13-14). Bat and baT haplotypes do not appear to distinguish susceptibility.

The specification teaches only the ERα and VDR haplotypes from humans. The specification is silent with regard to the analysis of these haplotypes in other mammalian species. The specification does not teach any correlative polymorphic sequences between human and other mammalian species in regard to these two genes. The specification does not show what the correlative sequence would be in other mammalian sequences. The specification does not indicate that the same haplotype pattern can be observed in other mammalian species.

The specification teaches the preferred method of treatment is prescribing or administering an agent that reduces the susceptibility of a subject to bone fracture (p. 15 lines 15-16). The specification lists examples such as administering sodium alendronate, parathryoid hormone, anabolic steroids, or vitamin D preparations (p. 15 lines 18-20). Treatment is dependent on polymorphism analysis, however, the specification does not provide a predictable association between px and baT alleles and bone fracture.

Working Examples

The specification provides an example which asserts the polymorphisms in the ERα gene and the VDR gene are positively correlated with increased susceptibility to bone fracture in human beings (p. 23 lines 1-4). The population studied was human subjects aged 55 years or older living in the Ommoord district of the city of Rotterdam in

the Netherlands (p. 23 lines 7-8). The example provided by the specification is drawn to a population of 634 women (p. 29 lines 9-11). The specification does not indicate the racial breakdown of the population.

The specification teaches to use direct molecular haplotyping methods to determine the BsmI, ApaI, and TaqI RFLPs at the 3' end of the VDR gene and the PvuII and XbaI RFLPs in the first intron of the ERα gene (p. 24 lines 4-6).

The specification asserts the association of the px haplotype and the baT haplotype with regard to homozygous and heterozygous carriers (p. 27 lines 12-15). Of the 634 women with information regarding vertebral fractures the specification asserts there was an association between the px haplotype and lumbar spine BMD and therefore the px haplotype is considered a risk allele (p. 29 lines 9-11).

The specification teaches in the sample of 634 women in which vertebral fractures were available, the association between px and lumbar spine BMD showed a p value of 0.11 (p. 29 lines 10-12). It is unclear what would be considered a "risk allele", the association between px and lumbar spine BMD is not significantly significant.

There was no association between VDR haplotype baT and lumbar spine or femoral neck BMD but it was selected as a risk allele based on previous studies (p. 29 lines 13-14). The specification does not give the determining factors of a risk allele.

The specification asserts there was a significant allele-dose effect of px being associated with decreased lumbar spine BMD only for women homozygous for baT (p. 29 lines 16-19). The specification asserts that in a multivariate regression model there appears to be a borderline significant interaction between px and baT (p. 29, lines 23-

24). The p value for the multivariate regression model was p=0.09 which is not significantly significant (p. 29 line 23). The specification teaches similar associations were found in vertebral fractures, but the data is not presented (p. 29 lines 24-25). It is unclear if the association of px and baT with vertebral fractures has a p value which is significantly significant or if the association has a p value which is not significantly significant.

The specification does not teach a correlation between "any allele" of a vitamin D receptor and susceptibility to bone fracture. The specification does not indicate that having only a "b" allele or only an "a" allele or only a "T" allele would provide the skilled artisan with a predictable correlation to bone fracture.

The specification teaches the number of women with vertebral fractures broken down into ERα genotype groups (Table 4 p. 30). Table 4 lists the p value as 0.0002 (Table 4 p. 30). It is unclear if the p value is a comparison of two genotype or if it is a comparison of all the genotypes combined. If it is a comparison of all the genotypes combined it is unclear what the p value association is actually describing.

With regard to ERα and VDR haplotypes and fracture risk, the specification teaches that in non-carriers and heterozygous carriers of VDR haplotype 1 (baT) no significant ERα haplotype 1 (px) genotype dependent differences were observed (p. 31 lines 4-6). Therefore, the specification teaches the only statistically significant association with regard to bone fracture risk appeared to be for subjects homozygous for VDR haplotype (baT), and also heterozygous or homozygous for ERα haplotype (px) (p=0.01). It is noted, however, that the racial breakdown of the subjects tested, is not

disclosed. Accordingly, it is unclear if this result is population specific, or if it applies to any subject, regardless of racial origin (i.e. Caucasian, vs. Asian, vs. African).

The unpredictability of the art and the state of the prior art

The art teaches unpredictability with regard to the relationship of ERα, VDR, and susceptibility to bone fractures. Aerssens et al. (Osteoporos International 2000 vol 11 p. 583) teaches a study which measure ERα and VDR allele frequencies between well defined groups of osteoporotic hip fracture patients and elderly healthy controls (p. 583 2nd column last paragraph). Aerssens et al teaches the use of two populations of Caucasian women, over 60 years of age (p. 584 1st and 2nd paragraph Materials and methods). Aerssens et al teaches the use of the BsmI site in VDR and either the PvuII or XbaI site in ER (p. 585 1st columns 1st and 2nd paragraph). Aerssens et al teaches that no consistent statistical relationship could be identified between VDR and ERα gene polymorphisms and the phenotypic parameters of BMD and biochemical markers of bone turnover and that these findings do not support the hypothesis that VDR or ERα polymorphisms are associated with osteoporotic hip fracture (p. 589 1st column Discussion). Aerssens et al teaches there is no significant relationship of VDR polymorphisms with hip fracture (p. 589 Discussion beginning of last paragraph in 1st column). Aerssens et al teaches the ERα genotype distribution between elderly controls and women with osteroporotic hip fractures were not significantly different (p. 589 last paragraph).

However, Kobayasi et al (Maturitas 2002 Vol 41 p. 193) teaches the PvuII and

XbaI polymorphisms of the ERα gene were associated with BMD in postmenopausal Japanese women and these polymorphisms can be used as genetic markers for predicting vertebral fracture (Abstract). Kobayasi et al teaches the use of a population of 569 Asian woman for a assessment of vertebral fractures (p. 194 Subjects 1st paragraph and last paragraph of the page). Kobayasi et al teaches the genomic analysis of samples using both PvuII and XbaI (p. 195 Genomic DNA Analysis). Kobayasi et al teaches the PPxx genotype is associated with low lumbar spine BMD in Japanese subjects (p. 197 2nd column). Kobayasi et al teaches the frequency of PPxx genotype tended to be higher in the fracture group than in the non-fracture group and the PPxx genotype is a useful genetic marker not only for predicting low bone mass but also for predicting the risk of vertebral fracture (p. 198 2nd column end of 2nd paragraph) in contrast to the results of the instant specification. Kobayasi et al and Aerssens et al teachings indicate the association between haplotypes and susceptibility to bone fracture is population specific and not predictive in any population.

Van Meurs et al (Human Molecular Genetics 2003 Vol 12 p. 1745) teaches a study investigating the influence of genetic variation of the ER gene on 2042 individuals of the Rotterdam population (Abstract). Van Meurs et al teaches analyzing the PvuII and XbaI RFLPs of the ERα gene (Abstract). Van Meurs et al teaches a comparison with other Caucasian populations showed similar haplotype frequencies, but the haplotype frequencies found in Asian and African populations were different (Abstract). Van Meurs et al teaches the association of ERα polymorphisms with vertebral fracture risk was not observed in men (Abstract). Therefore the results of Van Meurs et al.

indicate the association of the haplotype of the ERα gene are population specific in regard to both population and sex.

The art teaches the combination of the three alleles in a single haplotype of VDR suggests association to bone fractures not a single allele of the VDR. Uitterlinen et al (Journal of Bone and Mineral Research 2001 Vol. 16 p. 379) teaches that analyzing only the BsmI (b haplotype) can compromise the outcome of studies because heterogeneous groups are compared. The extensive linkage disequilibrium at the 3' end of VDR gene can be measured accurately by the molecular haplotyping of three RFLPs, BsmI, ApaI (a haplotype), and TaqI (t haplotype). Uitterlinden et al. teaches the haplotypes, which by themselves are not functional polymorphisms, can be used as markers for truly functional polymorphisms elsewhere in the 3' end of the VDR gene (p. 383 1st column 1st paragraph).

The art teaches that results are population study specific and the relationship between ERα and VDR is not fully understood. Wiling et al (Journal of bone and mineral research 1998 Vol. 13 p. 695) teaches different studies have identified different associations between the ERα genotype and BMD or ERα and osteoporosis (p. 700 last paragraph and p. 701 1st paragraph). Wiling et al teaches differences in association may reflect founder effects, which would lead to differences in the distribution of alleles among population groups (p. 700 last paragraph and p. 701 1st paragraph).

Wiling et al teaches the mechanism of the interaction between the VDR and the ERα gene is not known (p. 702 2nd column 2nd full paragraph). Wiling et al teaches that there might be a functional link between the ERα and VDR for which the intragenic sites

are acting as markers but the actual link between the two genes is not known (p. 702 2nd column 2nd full paragraph). The teaches of Wiling et al. indicate that there is a variation of results with regard to association studies of VDR and ERα and differences between the studies might be due to population effects.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there are a significant number of parameters which would have to be studied. The skilled artisan would have to test each species of mammals individually to determine if the alleles presented exist in other species and if the alleles do exist in other species if the same combination of haplotype would give similar results in regard to susceptibility of bone fracture. The skilled artisan would have to test every possible allele and combination of alleles and also test in different populations with representative controls to determine which specific alleles or combination of alleles would give results to susceptibility of bone fracture.

This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where haplotype and alleles are provided but there is no support in the art or the specification for the use in mammalian subjects and the unpredictability teachings in the art with regard to alleles and haplotypes associated with the susceptibility of bone fractures. The unpredictable teachings in the art with regard to alleles and haplotypes associated with different population. Given there is no support in the art or the specification for the relationship of px with susceptibility of bone fracture in any population. Given there is no support in the art or the specification for any allele of VDR to be associated with susceptibility of bone fracture. Given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. Though the claims are rejected above as not being enabled the following 102 and 103 rejections are being made in the interest of compact prosecution of the application.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 8-10, 12-13, 19-20, 25, and 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Willing et al. (Journal of bone and mineral research 1998 Vol 13, p. 695).

Willing et al. teaches the association of a risk of bone fracture with the BsmI region of VDR and the XbaI and PvuII regions of ERα. With regard to Claims 1, 2, 10, 12, 13 Willing et al teaches that there was an association between women who were homozygous ppxx and lumbar spine and total body BMD levels (Abstract and Table 4). Willing et al teaches that low bone mineral density is a risk factor for osteoporosis and related fractures (Introduction 1st paragraph). With regard to Claim 3, Willing et al teaches the BsmI restriction site was analyzed (Vitamin D Receptor p. 697). Willing et al teaches that women with a pp genotype and a bb VDR genotype exhibited a high average BMD (p. 699 1st column 1st full paragraph). With regard to Claims 8 and 9, Willing et al teaches performing genotyping from dot blots (whole blood collected on a filter paper) (Materials and Methods Subjects p. 696). With regard to Claims 19 and 20, Wiling et al teaches the use of a population of women (Materials and Methods Subjects p. 696).

With regard to Claim 25, Willing et al. teaches a nucleic acid primer molecule for amplification of the ERα gene, a means to determine the px haplotype, and a correlation between the px haplotype and risk of bone fracture (Table 4, Table 1, and Abstract), therefore Willing et al. teaches all the limitations of a kit.

With regard to Claim 29, Wiling et al teaches the amplification of the intragenic polymorphic region of the ER followed by restriction digestion (Estrogen receptor p.

697). With regard to Claim 30, Willing et al teaches the amplification of the intragenic polymorphic region of the VDR followed by restriction digestion (Vitamin D receptor p. 697).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 4-5, 14-15, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willing et al. (Journal of bone and mineral research 1998 Vol 13, p.

695) in view of Uitterlinden et al (Journal of bone and mineral research 2001 Vol. 16 p. 379)

With regard to Claims 1, 2, 10, 12, 13 Willing et al teaches that there was an association between women who were homozygous ppxx and lumbar spine and total body BMD levels (Abstract and Table 4). Willing et al teaches that low bone mineral density is a risk factor for osteoporosis and related fractures (Introduction 1st paragraph). With regard to Claim 3, Willing et al teaches the BsmI restriction site was analyzed (Vitamin D Receptor p. 697).

Willing et al, however, does not teach the use of the vitamin D receptor gene sites of ApaI and TaqI.

Uitterlinden et al. teaches the interaction between VDR and susceptibility for fracture. With regard to Claims 4-5 and 14-15, Uitterlinden et al teaches that in a study of the Rotterdam population the baT haplotype was overrepresented among fracture cases and can be used as a genetic marker for osteoporotic fracture in women independent of BMD (p. 380 Study subjects and Abstract).

With regard to Claim 26, Uitterlinden et al teaches a nucleic acid primer molecule for amplification of the VDR gene, a means to determine the baT haplotype, and a correlation between the baT haplotype and risk of bone fracture (p. 381 1st paragraph and Table 3), therefore Uitterlinden et al. teaches all the limitations of a kit.

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Willing et al. to further include ApaI and TaqI as taught by Uitterlinden et al. The ordinary artisan would have

been motivated to improve the method of Willing et al. to include ApaI and TaqI taught by Uitterlinden et al. because Uitterlinden et al. teaches analyzing only the BsmI can compromise the outcome of studies because heterogeneous groups are compared. Uitterlinden et al. teaches the extensive linkage disequilibrium at the 3' end of VDR gene, can be measured accurately by the molecular haplotyping of three RFLPs, BsmI, ApaI, and TaqI. Uitterlinden et al. Teaches the haplotypes which by themselves are not functional polymorphisms, can be used as markers for truly functional polymorphisms elsewhere in the 3' end of the VDR gene (p. 383 1st column 1st paragraph).

Conclusion

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Katherine Salmon 3/6/2006
Katherine Salmon
Examiner
Art Unit 1634

Jehanne Sitton
JEHANNE SITTON
PRIMARY EXAMINER
3/6/06